09-08-03

AF/1637

Docket No: AM100012OX1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	MARK et al.		
Application No.:	09/425,501	Group Art No.:	1637
Filed:	October 22, 1999	Examiner:	CHUNDURU
For:	PABLO, A POLYPEPTIDE THAT INTERACTS WITH BCL-XL AND USES RELATED THERETO		
Confirmation No.:	9642		
Customer Number:	25291		

Mail Stop Appeal Brief-Patents
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION - 37 CFR 1.192)

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on May 5, 2003.

2. FEE FOR FILING APPEAL BRIEF
Pursuant to 37 CFR 1.17(c), the fee for filing the Appeal Brief is $320.00.

3. EXTENSION OF TERM
The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply.

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EV 238504860 US addressed to the Commissioner for Patents, Mail Stop Appeal Brief-Patents, PO Box 1450, Alexandria, VA 22313-1450.

9/5/03
Date

Elizabeth Ruzich
Elizabeth Ruzich

(complete (a) or (b) as applicable)

(a) ☒ Applicant petitions for an extension of time for the total number of months checked below.

☐	One Month.	Fee in the amount of	$	110.00
☒	Two Months.	Fee in the amount of	$	410.00
☐	Three Months.	Fee in the amount of	$	930.00
☐	Four Months.	Fee in the amount of	$	1,450.00
☐	Five Months.	Fee in the amount of	$	1,970.00

If an additional extension of time is required, please consider this a petition therefor.

(Check and complete the next item, if applicable)

☐ An extension for months has already been secured and the fee paid therefor of $0.00 is deducted from the total fee due for the total months of extension now requested.

☒ Extension fee due with this request: $410.00

(b) ☐ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

4. TOTAL FEE DUE

THE TOTAL FEE DUE IS:	
Appeal brief fee	$320.00
Extension fee (if any)	410.00
TOTAL FEE DUE:	$730.00

5. FEE PAYMENT

☒ Charge fee to Deposit Account No. 07-1060. This is a request to charge for any additional extension and/or fee required or credit for any excess fee paid. A duplicate of this petition is attached.

Gavin Bogle

Limited Recognition Under 37 C.F.R. §10.9(b)

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (617) 665-8079
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9/5/03
Date

Elizabeth Ruzich
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APPEAL BRIEF

As set forth in the notice filed May 5, 2003 and received by the U.S. Patent Office on May 5, 2003, Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the pending claims. Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of the claimed subject matter.

09/11/2003 RMEBRAHT 00000037 071060 09425501
01 FC:1402 320.00 DA

09/11/2003 RMEBRAHT 00000037 071060 09425501
02 FC:1252 410.00 DA

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TABLE OF AUTHORITIES

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Wyeth.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative, or the assignees, which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 43, 44 and 49-65 are pending in the application. The pending claims are all on appeal and are set forth in Appendix A of this Brief.

IV. STATUS OF THE AMENDMENTS

A Final Office Action was mailed February 5, 2003, rejecting all pending claims of the instant application. A Notice of Appeal was filed on May 5, 2003, and received by the U.S. Patent Office on May 5, 2003.

V. SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the discovery of protein and polypeptides derived therefrom, which interact with Bcl-xL. These proteins are useful as modulating agents in regulating a variety of cellular processes.

Applicants' invention pertains to nucleic acid molecules comprising nucleotide sequences encoding an isolated human Bcl-xL binding protein comprising the amino acid sequence as set forth in SEQ ID NO: 2 (see, e.g., page 29, line 29 through page 30, line 6). The invention also pertains to the isolated nucleic acid sequence as set forth in SEQ ID NO: 1 (see, e.g., page 19, line 1 through page 19, line 21). The Bcl-xL binding protein modulates apoptosis (see, e.g., the specification at page 73, lines 9-11). The invention further pertains to variants of the isolated human Bcl-xL binding protein which have a high degree of homology to SEQ ID NO: 2 and to nucleic acids which encode fragments of the Bcl-xL binding protein which retain its binding activity (see, e.g., page 99, lines 14-16). The invention further pertains to genetically engineered host cells transfected, transformed or infected with the vector. These embodiments find support in the specification, e.g., at page 47, lines 10-15. The invention further

pertains to neuronal cell lines stably expressing a Pablo polypeptide or an isolated Bcl-xL binding protein as set forth in SEQ ID NO: 2. These embodiments find support in the specification, e.g., at page 57, line 29 through page 58, line 8. The invention further pertains to isolated nucleic acid molecules comprising a nucleotide sequence encoding an isolated mammalian fusion protein having an amino acid sequence of SEQ ID NO: 2, wherein the protein modulates apoptosis (see, e.g., page 48, lines 14-28).

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Applicants present the following issues for review:

I. Whether the subject matter of claims 43, 44, 49, 50, 51, 54, 55, 56, 57, 58, 59, 60, 61, and 65 are patentable in light of Nagase et al.

II. Whether the fragments of claims 52, 53, 62, 63, and 64 are supported by adequate written description, and are patentable in light of Nagase et al.

VII. GROUPING OF CLAIMS

Applicants respectfully submit that the pending claims do not stand or fall together. Applicants have grouped the claims into two separate sections. The discussion of why the claims do not stand or fall together can be found in the Arguments section under the heading: Grouping of Claims.

VIII. ARGUMENTS

Claim Rejections Under 35 U.S.C. §102(b) for Full-Length Sequence

Claims 43, 44, 49, 51, 54, 55, 56, 57, 59, 60, 61, and 65 stand rejected under 35 U.S.C. §102(b) as anticipated by Nagase et al. (DNA Res., *Prediction of the Coding Sequences of Unidentified Human Genes*, 3: 321-329, 1996; courtesy copy included in Appendix B). Applicants respectfully submit that Nagase does not anticipate the instant invention because Nagase does not provide an enabling disclosure because Nagase discloses no use whatsoever for the bare sequences disclosed. The standard for enablement is set forth in 35 U.S.C. §112, first paragraph:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same. [Emphasis added.]

To anticipate an invention a reference must provide an enabling disclosure, *In re Hoeksema*, 399 F.2d 269, 273 (CCPA 1968). The Examiner states (Appendix C, paper no. 24, page 3) that the "enablement issue is not relevant in the present context." Applicants respectfully disagree. It is black letter law that a reference must enable the claimed invention to be considered anticipatory (*Hoeksema* at 1499-1500). In *Hoeksema* a reference was found to not anticipate, because the reference only disclosed the primary structure of the chemical. The prior art disclosure was considered merely a mental concept and a formula on paper, and thus non-enabling. See also *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 555 (1870):

> Patented inventions cannot be superseded by the mere introduction of a foreign publication of the kind, though of prior date, unless the description and drawings contain and exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. [Emphasis added.]

The primary structure of a protein is defined in the art as "the sequence of amino acids and location of disulfide bridges, if there are any" (Stryer, L., Biochemistry, 32 (5th ed. 1981); a courtesy copy of the relevant page is provided in Appendix B). Nagase only discloses the primary structure of the DNA and discloses no use at all for that DNA and so the situation is therefore analogous to *Hoeksema*. It follows that Nagase does not anticipate the rejected claims. Furthermore, because Nagase merely provided a primary structure without an indication of a use for the invention, Nagase does not provide an enabling disclosure of the instant invention and therefore does not anticipate the present invention.

Nagase does not suggest that the peptide encoded by the disclosed DNA will bind to Bcl-xL or that the peptide will modulate apoptosis. Nagase does not disclose how to use the invention at all. Nagase does not provide an enabling disclosure and therefore does not put the public in possession of the invention. As stated by the court in *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962):

> [The reference must] exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. Mere vague and general representations will not support such a defense, as the knowledge supposed to be derived from the publication must be sufficient to enable those skilled in the art or science to understand the nature and operation of the invention and to carry it into practical use. Whatever may be the particular circumstances under which the publication takes place, the account publication takes place, the [sic] to support such a defense, must be an account of a complete and operative invention capable of being put into practical operation. [Emphasis added.]

The Examiner views Nagase as an anticipating reference because he claims Nagase is operable (Appendix C, paper no. 24, page 2). In the Examiner's view, operability is contingent upon the ability to synthesize the invention given a combination of the reference and the knowledge in the art. The Examiner cites the MPEP at 2121.02 for support, which states that: "One of ordinary skill in the art must be able to make or synthesize [the invention]." Applicants are not refuting the ability of one skilled in the art to synthesize the sequence given the teaching in Nagase. Rather, Applicants point out that the ability to make or synthesize the invention does not displace the requirement that a reference must be enabling for the invention and that enablement requires a disclosure of how to make *and use* the invention.

The cases cited by the Examiner are not on point and merely show that in the chemical arts the utility of an invention is often well established, while the synthesis of compounds is difficult. In the biotechnology arts, the synthesis is often not problematic but clearly the enablement and utility requirements of 35 U.S.C. §112, first paragraph may be. The process for making DNA is not in dispute. The issue is whether the primary chemical structure or "name" of the particular DNA molecule is sufficient to contain an enabling disclosure, which it is not. The mere mention of the primary structure of the DNA molecule, alone, is not enabling.

Claim Rejections Under 35 U.S.C. §102(b) for Fragments

Claims 52, 53, 62, 63, and 64 stand rejected under 35 U.S.C. §102(b) as anticipated by Nagase. Applicants respectfully disagree. Even if Nagase is found to anticipate the full length sequence, and applicants do not concede that it does, the fragments disclosed are patentable over the full length sequence because as stated in *Messerschmidt* v. *U.S.*, 29 Fed. Cl. 1, 21 (Fed Cl. 1993), "a prior art reference to a genus anticipates no species which discloses a novel invention." Nagase provides no disclosure of the structure of any useful fragments. The fragments are patentably distinct from the full-length sequence because they contain the specific binding sites that modulate apoptosis while Nagase makes no suggestion of any binding sites or the sequence's function as a modulator of apoptosis. The patentability of a species over a genus is further illustrated in *Minnesota Mining v. Johnson & Johnson*, 976 F.2d 1559, 1572 (Fed. Cir. 1992):

> The Master found no anticipation because the Straube patent does not include any mesh size or thickness parameter for the knit fiberglass fabric substrate mentioned in the Garwood claim. The Master found that the ranges 3M extrapolated from Straube are "so broad as to be meaningless to one skilled in the art. The Straube patent provides no guidance as to how to construct a fiberglass cast with the beneficial properties achieved by the Garwood invention; strength, porosity, lightness, and ability to cure quickly." The Master recognized that although Garwood's specific claims are subsumed in Straube's generalized disclosure of knit fiberglass as a substrate, this is not literal identity. [Emphasis added.]

Nagase has disclosed a segment of DNA but has not pointed the way to the claimed fragments, which encode the binding domain for Bcl-xL. Nagase, therefore, does not put one skilled in the art in possession of the useful and specific fragments claimed.

Claim Rejections Under 35 U.S.C. §112 First Paragraph

While it is unclear which claims the Examiner is rejecting, Applicants believe claims 50, 52-53, 55, 58 and 62-65 stand rejected under 35 U.S.C. §112 first paragraph.

a. Hybridization

Claims 50, 55 and 58 are herein treated as rejected with respect to their hybridization language.

The Examiner rejects the hybridization claims (Appendix C, paper no. 21, page 5) as lacking "description of fragments or complementary nucleic acid sequence [sic] that

hybridize to SEQ ID NO: 1." He further asserts (Appendix C, paper no. 24, page 4) that, "[b]y permutation and combination, there would be over several thousand possible fragments, if not millions." In response, Applicants refer to the PTO Synopsis of Application of Written Description Guidelines[1]. Therein, the PTO states at page 36 that an invention is adequately described when: "the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function." Their example of "highly stringent hybridization conditions" at page 38 is "6XSSC and 65 degrees Celsius."

Claims 50, 55, and 58 meet the requirements of the Written Description Guidelines. Claim 50 states that the "nucleotide sequence hydridizes to the complement of a nucleotide sequence set forth in SEQ ID NO: 1 which encodes a Bcl-xL binding protein" under the highly stringent conditions of "6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C." As stated in *Enzo* at 1327 "claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Therefore the Applicants respectfully request the reversal of this rejection.

b. Fragments

Claims 52-53, and 62-65 are herein treated as rejected with respect to claiming fragments encoding a Bcl-xL binding domain.

The Examiner objects to the fragment claims (Appendix C, paper no. 21, page 4) because "[t]he recitation of amino acids 419-559 or 429-559 in [sic] Bcl-xL binding domain in claim 2 do not specify the exact site for binding. Further no information is given regarding a methodology to determine such common elements or attributes. Further, there is no description of fragments." The Examiner has provided no evidence to support these assertions. As stated in the application on page 9, "[p]referred Bcl-xL binding domains are approximately 120-150 amino acid residues in length." The Examiner also states at page 9 that the "Pablo Bcl-xL binding domain comprises from

[1] The Guidelines were cited with approval by the Court of Appeals for the Federal Circuit in *Enzo*

about amino acid 419 to about amino acid 559 or about amino acid 429 to about amino acid 559 of SEQ. ID NO:2." The Examiner also states (Appendix C, paper no. 24, page 4) that the "[s]pecification cannot be read into the claims." The function of the specification in this instance, however, is to support the claims. It is not an issue of the specification being the source of limitations that are being read into the claims because the claims specify the binding domain as 419-559 or 429-559, where the binding protein fragment modulates apoptosis. Applicants respectfully request the reversal of this rejection.

Claim 65 is rejected through its dependency to the independent claim 52. Examiner misstates the dependence, however, as claim 65 is independent. Reversal of this rejection is requested.

Policy

Applicants believe that the Examiner has placed too much emphasis on case law related to chemical inventions. Applicants respectfully point out that as a biotechnology case, this application presents a good opportunity for the USPTO to depart from the narrow framework provided by chemical case law.

It is well known that modern biotechnology law has evolved from a heritage of chemical case law. E.g., in a case involving DNA and cDNA from human and bovine heparin-binding growth factors (*In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)), the basis for a prima facie case of obviousness was considered using an example of *chemists* creating compounds with similar properties with respect to homology, analogs, and isomers. In the biotechnology case *Enzo* at 1329, steroids were described only in terms of their ability to lessen inflammation as an example of insufficient written description.

The law, however, has evolved differently for the chemical arts and for the biotechnology arts in some situations. The cases involving written description and utility provide examples of this departure. E.g., *Enzo* at 1326 states that a biological deposit may be necessary to satisfy written description and enablement requirement for claims to microorganisms because it is possible for the description of how to make the invention to

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Biochem, Inc. v. *Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002)

be inadequate to make the claimed invention. Indeed a deposit may be sufficient to satisfy these requirements (*Enzo*, 1326). Deposits are not relevant in chemical cases because the formula of the compound and a description of how to make it are generally sufficient.

In re Schoenwald, 964 F.2d 1122 (Fed. Cir. 1992) is a chemical case argued on 35 U.S.C. 101 grounds which found that a utility was not required to be disclosed for prior art to be anticipating. The reasoning in *Schoenwald* should not be applied to the instant application as the applicant in that case did not dispute that the prior art was enabled (*Schoenwald*, 1122).

The court in *Schoenwald* found that the use of a chemical compound is inherent to its structure and therefore the discovery of a new use "can not impart patentability to claims to the known composition" (*Schoenwald*, 1124). This rational, however, should not be applied to the biotechnology arts because isolated DNA does not have any intrinsic function. One cannot know the function of a sequence by looking at the DNA, as one can with chemicals. This is the reason the utility and written description guidelines were promulgated. The utility of isolated DNA is that it encodes information that cannot be deduced from the sequence alone but which, when combined with other knowledge, can define a patentable invention. Unlike a small organic molecule, which has an intrinsic and perhaps undiscovered use, the sequence of an isolated molecule of DNA, without more, has no use at all.

Other aspects of the law are similar for the chemical arts and biotechnology arts, but require a slightly different application. The issue of enablement falls into this category. The "make and use" components of enablement provide an analogous but not identical situation for chemicals and DNA. A claim for a chemical compound may not be enabled, because the specification does not teach a person of skill in the art to *make* the compound. Similarly, a claim for a DNA compound may not be enabled because the specification does not teach how to *use* the molecule.

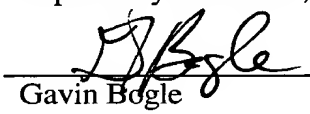
Grouping of Claims

The claims have been divided into two groups: Group I includes claims to the full-length sequences and claims reciting hybridization, and Group II includes claims to fragments. Claims to the fragments do not stand or fall with the claims for the full-length sequence and claims for hybridization, because the claims to fragments can be viewed as a species where the full-length sequence is the genus. A species is separately patentable from the genus because it is a novel invention. The claims for fragments involve different facts and different rejections than the claims involving full-length sequences and hybridization language. Even if Group I claims are found to be unpatentable, Group II claims could still be found patentable.

VII. CONCLUSION

Appellants submit that the pending claims 43-44 and 49-65 are patentable. It is respectfully requested that the Board reverse the final rejection of the subject matter of these claims for the reasons given above.

Respectfully submitted,



Gavin Bogle

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Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (617) 665-8079

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Appendix A

Pending Claims

43. A recombinant expression vector comprising a polynucleotide encoding a Pablo polypeptide comprising the amino acid sequence of SEQ ID NO:2.

44. A genetically engineered host cell, transfected, transformed or infected with the vector of claim 43.

49. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an isolated human Bcl-xL binding protein, wherein said isolated human Bcl-xL binding protein has 98% amino acid sequence identity with a Bcl-xL binding protein set forth in SEQ ID NO:2.

50. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an isolated human Bcl-xL binding protein, wherein said nucleotide sequence hybridizes to the complement of a nucleotide sequence set forth in SEQ ID NO:1 which encodes a Bcl-xL binding protein in 6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

51. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an isolated human Bcl-xL binding protein as shown in SEQ ID NO:1.

52. A nucleic acid molecule comprising a nucleotide sequence encoding an isolated human Bcl-xL binding domain, wherein said domain is a fragment of the nucleic acid molecule as shown in SEQ ID NO:1.

53. The isolated nucleic acid molecule of claim 52 wherein the isolated Bcl-xL binding domain consists of amino acids 419-559 or amino acids 429-559 of SEQ ID NO:2.

54. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an isolated human Bcl-xL binding protein, wherein said isolated human Bcl-xL binding protein modulates apoptosis.

55. The isolated nucleic acid molecule of claim 50, wherein said isolated human Bcl-xL binding protein modulates apoptosis.

56. The isolated nucleic acid molecule of claim 51, wherein said isolated human Bcl-xL binding protein modulates apoptosis.

57. The isolated nucleic acid molecule of claim 49, wherein said nucleic acid molecule encodes a fusion protein.

58. The isolated nucleic acid molecule of claim 50, wherein said nucleic acid molecule encodes a fusion protein.

59. The isolated nucleic acid molecule of claim 51, wherein said nucleic acid molecule encodes a fusion protein.

60. A neural cell line stably expressing a heterologous Pablo polypeptide or an isolated Bcl-xL binding protein set forth in SEQ ID NO:2.

61. An isolated nucleic acid molecule comprising a heterologous nucleotide sequence encoding an isolated mammalian fusion protein having an amino acid sequence of SEQ ID NO:2, wherein the protein modulates apoptosis.

62. The isolated nucleic acid molecule of claim 52, wherein said isolated human Bcl-xL binding protein fragment modulates apoptosis.

63. The isolated nucleic acid molecule of claim 62, wherein said isolated human Bcl-xL protein fragment comprises from about amino acid 419 to about amino acid 549 of SEQ ID NO:2.

64. The isolated nucleic acid molecule of claim 62, wherein said isolated human Bcl-xL protein fragment comprises from about amino acid 429 to about amino acid 559 of SEQ ID NO:2.

65. An isolated nucleic acid molecule comprising a nucleotide sequence, wherein said isolated human Bcl-xL binding protein has greater than 91% nucleic acid sequence identity with a Bcl-xL binding protein set forth in SEQ ID NO:1.

DNA RESEARCH 3, 321–329 (1996)

Prediction of the Coding Sequences of Unidentified Human Genes. VI. The Coding Sequences of 80 New Genes (KIAA0201-KIAA0280) Deduced by Analysis of cDNA Clones from Cell Line KG-1 and Brain

Takahiro NAGASE, Naohiko SEKI, Ken-ichi ISHIKAWA, Miki OHIRA, Yutaka KAWARABAYASI, Osamu OHARA, Ayako TANAKA, Hirokazu KOTANI, Nobuyuki MIYAJIMA, and Nobuo NOMURA*

Kazusa DNA Research Institute, 1532-3 Yana, Kisarazu, Chiba 292, Japan

(Received 4 October 1996; revised 24 October 1996)

Abstract

In this series of projects of sequencing human cDNA clones which correspond to relatively long and nearly full-length transcripts, we newly determined the sequences of 80 clones, and predicted the coding sequences of the corresponding genes, named KIAA0201 to KIAA0280. Among the sequenced clones, 68 were obtained from human immature myeloid cell line KG-1 and 12 from human brain. The average size of the clones was 5.3 kb, and that of distinct ORFs in clones was 2.8 kb, corresponding to a protein of approximately 100 kDa. Computer search against the public databases indicated that the sequences of 22 genes were unrelated to any reported genes, while the remaining 58 genes carried sequences which show some similarities to known genes. Protein motifs that matched those in the PROSITE motif database were found in 25 genes and significant transmembrane domains were identified in 30 genes. Among the known genes to which significant similarity was shown, the genes that play key roles in regulation of developmental stages, apoptosis and cell-to-cell interaction were included. Taking into account of both the search data on sequence similarity and protein motifs, at least seven genes were considered to be related to transcriptional regulation and six genes to signal transduction. When the expression profiles of the cDNA clones were examined with different human tissues, about half of the clones from brain (5 of 11) showed significant tissue-specificity, while approximately 80% of the genes from KG-1 were expressed ubiquitously.

Key words: full-length cDNA sequence; mRNA expression; chromosomal location; myeloid cell line KG-1; brain.

1. Introduction

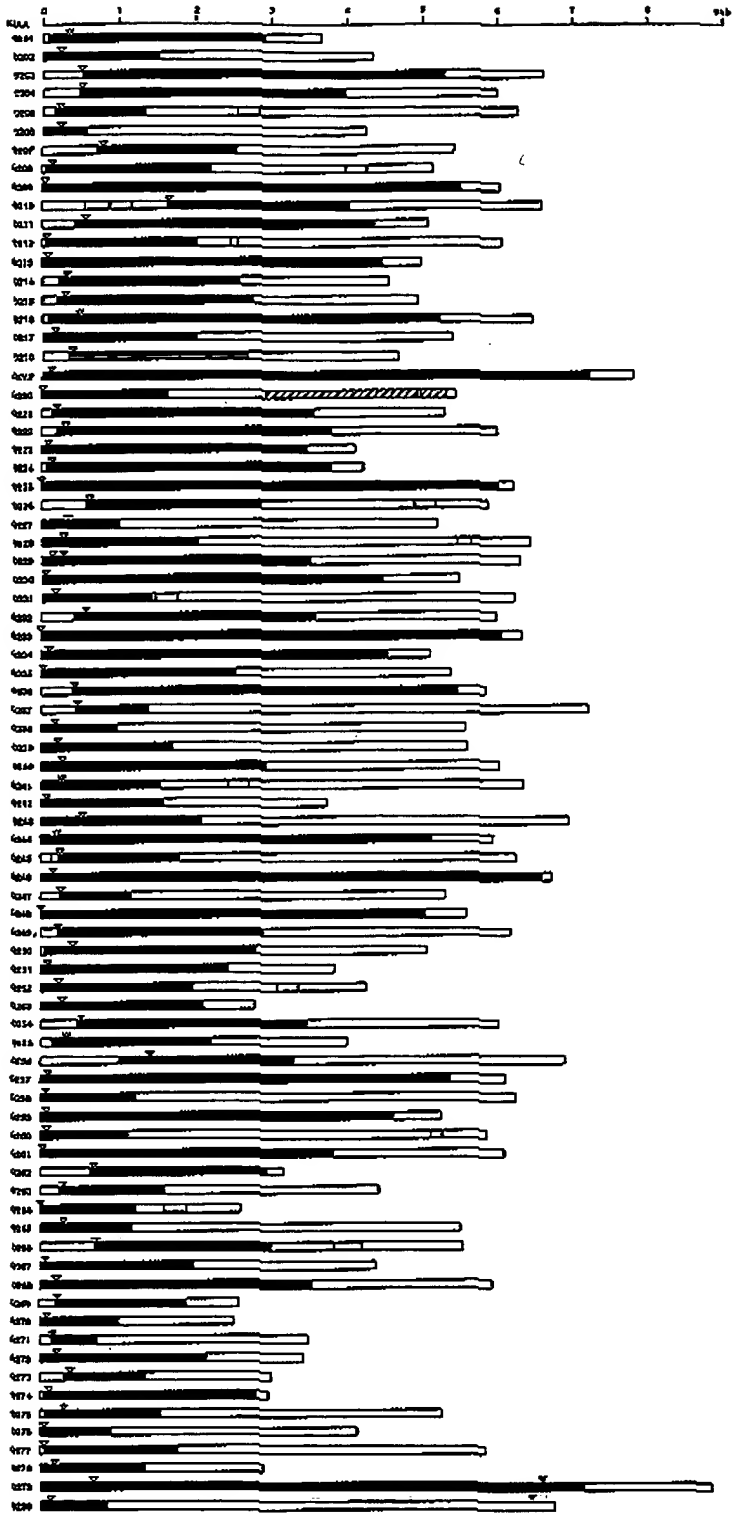
To accumulate information on the coding sequences of unidentified human genes, we have begun a project for sequencing the entire cDNA clones which correspond to relatively long and nearly full-length transcripts.[1,2] Whereas many genes of functional importance appear to be expressed in longer transcripts, little effort has been made to analyze such transcripts mostly due to technical difficulties. Although a large amount of expressed sequence-tags (ESTs) obtained by one path sequencing of cDNA libraries have been accumulated for comprehensive understanding of expression profiles, the information obtained is limited to relatively short cDNA species.[3–5] By our sequencing strategy, cDNA libraries enriched with clones corresponding to relatively long transcripts were constructed, and the clones that carry unreported terminal sequences are first selected. Then, the sizes of the mRNA corresponding to these clones are analyzed by Northern hybridization, and the entire nucleotide sequences of clones that comprised nearly full-length transcripts were determined. We have already predicted the coding sequences of 180 new genes from analysis of cDNA clones which were isolated from human immature myeloid cell line KG-1.[1,2] By computer search, 68 genes were found to be new, and most of the remaining genes (96 genes) were related to those with biologically important function. In this paper, we report the coding sequences of additional 80 genes and their sequence features as well as expression profiles.

2. Materials and Methods

The source of the KG-1 cDNA clones was identical to that used in the previous paper.[1] The brain cDNA clones were selected from a cDNA library which was constructed from a whole brain mRNA fraction of CLON-

Communicated by Mituru Takanami

* To whom correspondence should be addressed. Tel. +81-438-52-3930, Fax. +81-438-52-3931



Fifure 1 Physical maps of the 80 cDNA clones analyzed.

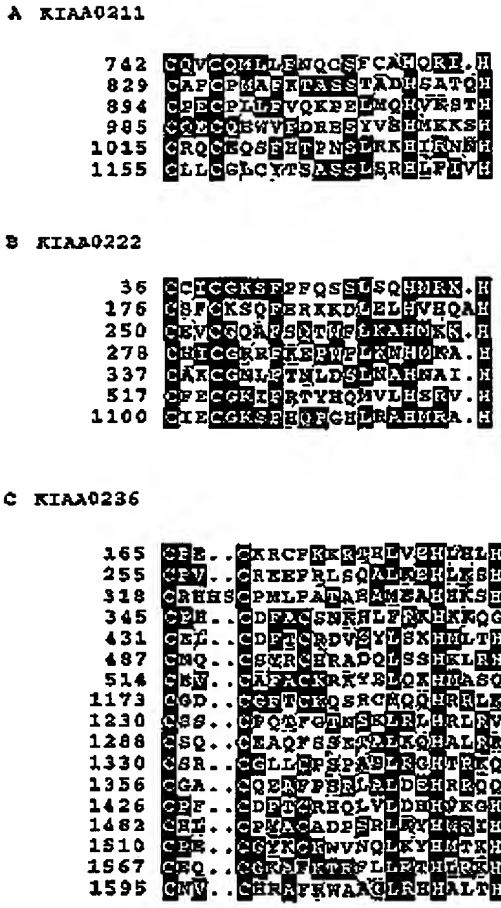


Fig. 2. Distinct C2H2 type zinc finger repeats in products encoded in genes: **A**, KIAA0211; **B**, KIAA0222 ; **C**, KIAA0236.

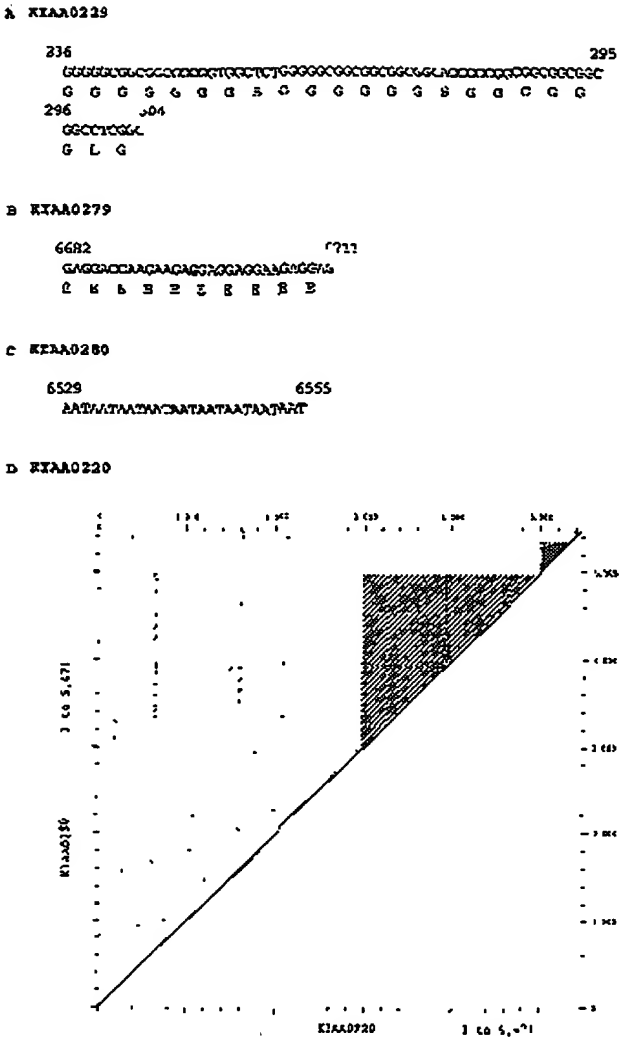


Fig. 3. Typical repeats observed in cDNA clones from identified genes. **A**, GGC repeats in KIAA0229: **B**, GAG repeats in KIAA0279: **C**, AAT repeats in KIAA0280: **D**, reiteration of two types of 55 nucleotide repeats in KIAA0220. In **A** and **B**, translated amino acids are indicated below the DNA sequences. Numerals above the sequences are nucleotide positions in each clone.

TECH (California, USA) by a method essentially identical to that used for the library of KG-1 cells. The methods used for selection of clones, Northern hybridization, sequence analysis, computer analysis of sequences and chromosomal mapping of cDNA clones were described previously.[1,6]

3. Results and Discussion

3.1. Sequence features of analyzed cDNA clones

As in the previous papers,[1,2] the cDNA clones carrying inserts longer than 2 kb were randomly selected from the libraries constructed from the medium-sized cDNA class, and both the terminal sequences were analyzed to select unidentified clones with poly(A) tails. The clones harboring inserts more than 90% of the length of the corresponding transcripts were further selected by northern hybridization, and their sequences were determined. Among 85 clones fully sequenced, 80 clones were

Figure 1. The horizontal scale represents the cDNA length in kb, and gene numbers are given on the left. Open reading frames (ORFs) within coding regions, untranslated regions, Alu sequences, and other repetitive sequences are indicated by solid, open, dotted, and hatched boxes, respectively. The details of repeats in KIAA0220 are shown in Fig. 3D. The positions of the first * ATG codon in each ORF are represented by open triangles. The solid triangles show the positions of the triplet repeats listed in Figs. 3A, B and C. The nucleotide sequence data reported in this paper were deposited in the GSDB, DDBJ, EMBL and NCBI nucleotide sequence databases under the accession numbers shown in Table 3.

Table 1. Genes with similarities to nucleotide and amino acid sequence database files.

Gene no. (KIAA)	Database files	Accession no.[a]	Identities (%)	Overlap[b] (amino acid residues)
0201	heat shock protein 105 kD alpha (M)	D67016	93.4	858
0202	KIAA0128 (H)	D50918	77.7	413
0203	coiled-coil protein CC1 (M)	X82318	84.4	141
0204	serine/threonine protein kinase Krs-1 (H)	U60206	30.5	483
0205	cosmid C01C10 (Ce)	U23526	28.0	344
0207	growth factor receptor-binding protein Grb10(M)	U18996	90.0	428
0208	dishevelled-3 (M)	U41285	98.7	681
0209	major CRK-binding protein DOCK180 (H)	D50857	62.3	1729
0210	cosmid B0393 (Ce)	Z37983	39.6	345
0211	finger protein 1 (H)	A32891[c]	23.2	343
0212	cosmid C47E12 (Ce)	Z68882	63.8	458
0214	cosmid ZK1248 (Ce)	U29244	35.2	739
0215	KIAA0239 (H)	D87076	60.4	312
0216	myosin heavy chain (R)	S21801[c]	22.5	900
0218	hypothetical 29.6 kD protein (E)	P27859[d]	30.1	204
0219	translational activator of GCN1 (Sc)	L12467	32.1	1888
0221	NAM7 (Sc)	P30771[d]	54.5	858
0222	finger protein MKR3 (M)	S03677[c]	23.9	323
0223	cosmid ZK669 (Ce)	Z37093	30.0	274
0224	putative ATP-dependent RNA helicase K03H1.2 (Ce)	P34498[d]	59.3	1064
0225	cosmid K12D12 (Ce)	Z49069	18.7	1301
0229	ankyrin 1 (H)	S08275[c]	21.7	652
0230	peroxidasin precursor (D)	U11052	38.0	1412
0231	adenylate cyclase (Sc)	S56776[c]	22.9	317
0233	cosmid T20D3 (Ce)	Z68220	33.9	427
0234	XE169 (H)	L25270	83.9	1363
0235	KIAA0099 (H)	D43951	81.5	850
0236	zinc finger protein ZNF142 (H)	U09849	98.8	170
0237	cosmid T10A3 (Ce)	U41035	40.4	228
0238	yolk sac permease-like molecule 1 (M)	U25739	38.7	223
0239	KIAA0215 (H)	D86969	60.4	311
0241	cosmid T26A5 (Ce)	U00043	45.8	164
0242	hypothetical 51.6kD protein ZK353.8 (Ce)	P34631[d]	25.3	351
0244	transcription elongation factor TFIIS (H)	X57198	29.6	161
0245	amino acid permease PRM1 (Sm)	L25068	40.9	480
0246	notch 3 (M)	X74760	27.5	299
0248	protein transport protein SEC7 (Sc)	P11075[d]	35.4	209
0249	KIAA0188 (H)	D80010	49.1	895
0251	cosmid C14H10 (Ce)	Z50863	24.0	407
0252	glutamic acid-rich protein precursor (Pf)	A54514[c]	18.3	503
0255	70kD endomembrane protein EMP70 (Sc)	P32802[d]	35.2	612
0257	cosmid C27F2 (Ce)	U40419	36.1	228
0259	rad4/cut5 protein (Sp)	P32372[d]	24.4	236
0260	cosmid C52E12 (Ce)	U50135	49.1	115
0261	parallel sister chromatids protein (D)	U40214	32.0	469
0263	hypothetical protein YD9335.01 (Sc)	S54638[c]	30.7	197
0266	hypothetical protein 5 (Sc)	S49634[c]	25.9	704
0267	Na+/H+ exchanger 2 (H)	A57644[c]	29.0	418
0268	C219-reactive peptide (H)	L34688	100[e]	136
0269	extensin-like protein (Zm)	S49915[c]	29.9	228
0271	transforming protein bcl-2 (H)	C37332[c]	45.1	164
0272	hypothetical C08B11.7 protein (Ce)	Q09444[d]	33.6	294
0274	hypothetical NO330 protein (Sc)	P42837[d]	35.1	655
0275	testican (H)	S33293[c]	49.0	358
0276	hypothetical protein L3111 (Sc)	S59316[c]	25.1	180
0277	CDC25 protein homolog (H)	L26584	26.4	235
0278	growth factor Arc (R)	U19866	92.4	396
0279	cadherin-related tumor suppressor hFat protein (H)	X87241	26.5	656

[a] EMBL/NCBI/GSDB/DDBJ database files are shown unless specified.
[b] The size of regions which show similarities.
[c] PIR database files
[d] SWISS-PROT database files
[e] A partial sequence spanning aa positions 592 -727 of KIAA0268 has been reported.
Ce, *Caenorhabditis elegance*; D, *Drosophila melanogaster*; E, *Escherichia* coli; H, human; M, mouse; Pf, *Plasmodium falciparum*; R, rat; Sc, *Saccharomyces cerevisiae*; Sm, *Schistosoma mansoni*; Sp, *Schizosaccharomyces pombe*; Zm, *Zea mays*.

Table 2. Genes with regions that matched motifs in the PROSITE database.

Motifs	Description	Gene number (KIAA)	References
HSP70 3	Heat shock hsp70 proteins family	0201	18
ATP GTP A	ATP/GTP-binding site motif A (P-loop)	0202, 0212, 0214, 0216 0221, 0222, 0224, 0250	19
PROTEIN KINASE ST	Protein kinases	0204, 0213	20
PROTEIN KINASE ATP	Protein kinases	0204, 0213	20
ZINC FINGER C2H2	Zinc finger, C2H2 type	0211, 0222, 0236	11
CYTOCHROME C	Cytochrome c family heme-binding site	0211, 0223	21
YBL055C-1	Hypothetical YBL055c/yjjV family	0218	22
YBL055C-2	Hypothetical YBL055c/yjjV family	0218	22
DEAH ATP HELICASE	DEAD and DEAH box families ATP-dependent helicases	0224	23
IG MHC	Immunoglobulins and major histocompatibility complex proteins	0233	24
GLYCOSYL HYDROL F1 1	Glycosyl hydrolases family 1	0237	25
CYTOCHROME P450	Cytochrome P450 cysteine heme-iron ligand	0246	26
EGF	EGF-like domain cysteine pattern	0246, 0279	27
AA TRNA LIGASE II 2	Aminoacyl-transfer RNA synthetases class-II	0248	28
ATPASE C	ATP synthase c subunit	0256	29
ATPASE ALPHA BETA	ATP synthase alpha and beta subunits	0257	29
ZINC FINGER C3HC4	Zinc finger, C3HC4 type	0262	12
PRENYLATION	Prenyl group binding site	0270	15
BCL2	Apoptosis regulator proteins, Bcl-2 family	0271	9
THYROGLOBULIN 1	Thyroglobulin type-1 repeat	0275	30
CADHERIN	Cadherins extracellular repeated domain	0279	10

found to contain distinct open reading frames (ORFs) and were subjected to further analysis. The ORFs and the first ATG codon in each ORF are shown in Fig. 1 by solid boxes and open triangles, respectively. In the figure, KIAA0201 to KIAA0268 represent the clones from the KG-1 cDNA library and KIAA0269 to KIAA0280 represent the clones from the brain cDNA library. In-frame termination codons upstream of the first ATG codon were identified in 38 clones, suggesting that at least half of the clones analyzed harbor the complete coding region.

The results of computer analysis with the GCG software package are shown in Tables 1 and 2, Figs. 2, 3 and 4 and in the figure in the Supplement section. Sequence features are summarized below.

1. Sequences of 22 genes were unrelated to any reported sequences in the database files, except for ESTs (GenBank release 96.0, August 1996). The remaining 58 genes carried sequences with at least some similarities to known genes (Table 1). The genes that we are particularly noted are as follows. KIAA0208 was a human homolog of mouse *dishevelled-3*[7] and KIAA0246 carried a sequence with considerable similarity to the *Notch* gene family,[8] both of which are known to mediate cell fate decisions during development. KIAA0271 showed significant similarity to the *bcl-2* gene family which plays important roles in apoptosis.[9] KIAA0279 was related to a gene involved in cell-to-cell interaction.[10]

2. Protein motifs that matched those in the PROSITE motif database were found in 25 genes (Table 2).

3. On the basis of the search data of similarity and protein motifs, at least seven genes were considered to be involved in transcriptional regulation. Those senen genes are KIAA0211, 0215, 0219, 0222, 0236, 0239 and 0262, in which KIAA0211, 0222 and 0236 carried the C2H2 type zinc finger[11] (Fig. 2) and KIAA0262 the C3HC4 type zinc finger.[12]

4. The search data of similarity and protein-motifs also suggested 6 genes, KIAA0204, 0209, 0213, 0231, 0277 and 0278, are relating to signal transduction: The product encoded in KIAA0231 harbors a leucine-rich domain with significant structural similarity to that of adenylate cyclase[13] (Fig. 4A), and that of KIAA0277 shows a high degree of sequence similarity to proteins encoded in the *CDC25, Sos1* and *Ste6* (Fig. 4B).[14]

5. Significant transmembrane domains were identified in 30 genes, 11 of which harbored multiple hydrophobic regions. It is also noted that KIAA0270 harbors a binding site of the prenyl group which is assumed to anchor to membranes.[15]

6. Three genes harbored triplet repeats, which were often correlated with genetic disorders:[16] GGC(Gly) repeats occurred 20 times within a 23-triplet stretch in KIAA0229 , GAG(Glu) repeats occurred 7 times in a 10-triplet stretch in KIAA0279, and 9 AAT repeats were detected in the 3′-untranslated region (UTR) of KIAA0280 (Figs. 3A, B and C).

7. Alu sequences were identified in the 5′-UTRs of 2 genes and in the 3′-UTRs of 12 genes, respectively. The presence of Alu in the 5′-UTR has already been reported by Yulug et al.[17] Although the mechanism for Alu integration is not fully understood yet, the

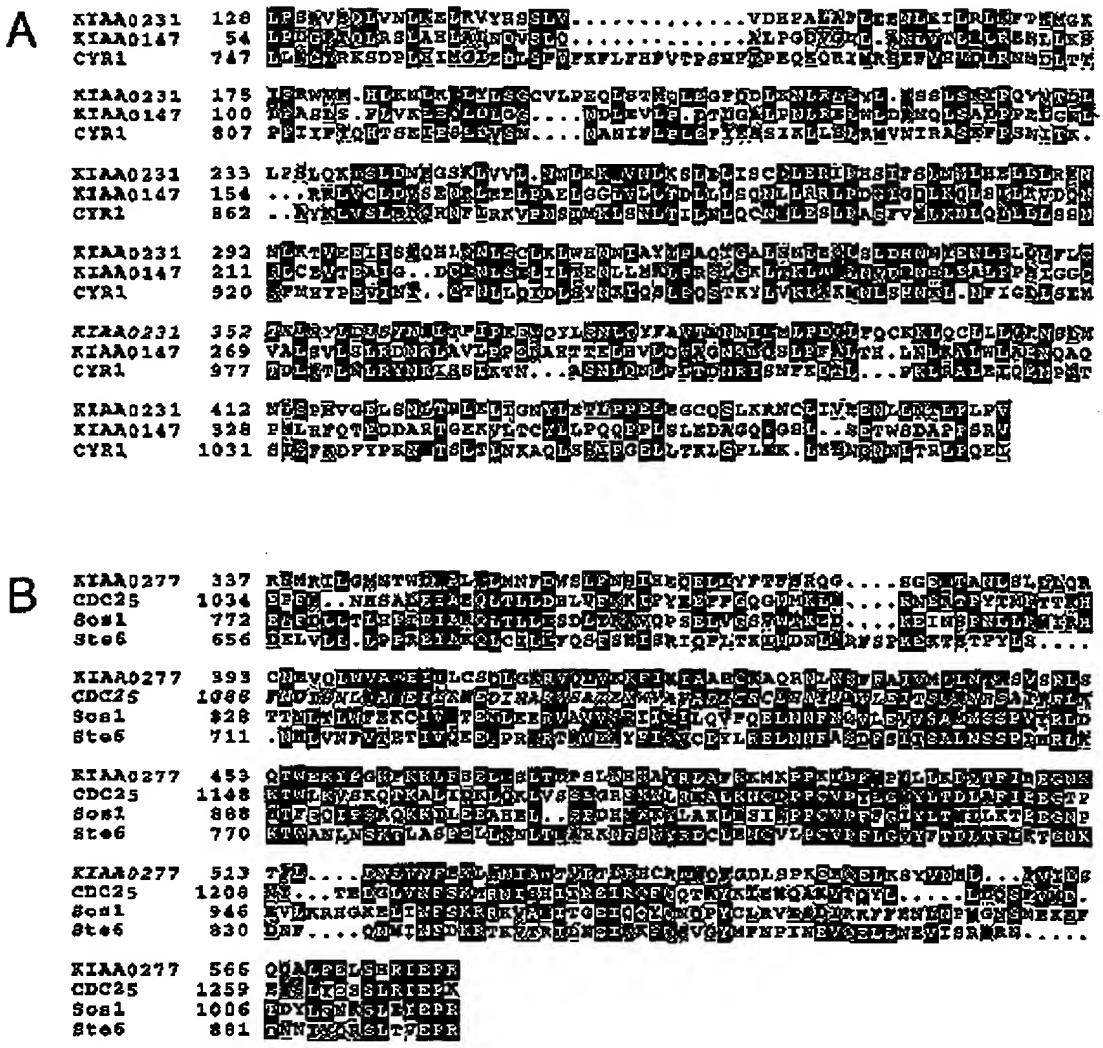


Fig. 4. Sequence comparison of (A) a leucine-rich domain in adenylate cyclase family and (B) *CDC25* gene family. Identical and similar amino acids are indicated by black and grey shading, respectively. Numerals represent the number of amino acid residues from the start codon.

lower occurrence rate of Alu in the 5′-UTR than 3′-UTR in cDNAs may be due to differences in the target size for Alu retroposition. It should be noted that the Alu sequence at the 5′-UTR of KIAA0245 overlaps the ORF, but as the first ATG in the ORF is present downstream of Alu, the Alu sequence does not seem to be translated.

8. Two repeated sequences, both of which are 55 nucleotides long, were found in KIAA0220 (Fig. 3D). They were reiterated 32 and 8 times, respectively, in the 3′-UTR of KIAA0220.

3.2. *Expression profiles in tissues*

The expression profiles of the sequenced genes were examined with 16 different human tissues and 2 cell lines including the KG-1 cell, and clear patterns were obtained for all but two clones. The results are summarized in Table 3. Seventy-nine percent (53 out of 67) of clones from the KG-1 cells and 36% (4 out of 11) of those from brain were found to be expressed ubiquitously, albeit to varying degrees, in all the tissues examined. Five out of 11 clones (45%) from brain were expressed specifically, if not exclusively, in brain. The patterns of two representative clones are shown in Figs. 5A and B. This is in sharp contrast to the fact that most of KG-1 clones exhibited ubiquitous expression. It was also noted that 10

Table 3. Summary of cDNA sequence data and expression patterns of identified genes in human tissues and cell lines.

Gene number (KIAA)	Total length of cDNA (bp)[a]	Amino acid residues	Expression[b]																Chromosomal[c] location	Accession[d] number
			KG-1	HeLa	He	Br	Pl	Lu	Li	Sk.m	Ki	Pa	Sp	Th	Pr	Te	Ov	Sm.i	Co	Pe.b		
0201[f,g]	3,614	858	+	+/−	+	++	+	++	+/−	+	+	+	+	−	−	++	+	+	+	+	13	D86956
0202[f,g]	4,344	508	+	+	+/−	++	++	++	+	+	+++	+	+	+	+	+/−	+	+	+	−	6	D86957
0203[e,f]	6,614	1,591	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	8,20,21	D86958
0204[f,g]	5,988	1,152	+	+	+	+	+	+	+	++	++	+	+	+	+	+	+	+	+	+	10	D86959
0205[e,f]	6,253	370	+	+	+	+	+	+	+	+	+	+/−	+	+	−	+	−	+	+/−	+	1,13	D86960
0206[e]	4,249	193	+	+	+/−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	5,11	D86961
0207[f]	5,431	588	+	++	−	−	+/−	+	+	+	+	+	+	+	+	+	+	+	−	−	7	D86962
0208[f]	5,146	693	++	++	+	+	++	++	+	+++	+++	+	++	++	++	++	+++	++	++	++	3	D86963
0209[f]	6,050	1,842	+	−	−	−	−	+	++	+	−	+	++	++	−	−	+	+	−	+++	6	D86964
0210[e,f]	6,611	795	+	+	+/−	+	+	++	+	+	++	+	+	+	+	+	+	+	+	+	3	D86965
0211[f,g]	5,086	1,267	+	+	+++	+	+	+	+	+++	+	+	+	+	+	+	+	+	+	+	15,18	D86966
0212[e,f,g]	6,072	657	++	+	+	+	+	+	++	−	+	++	+	++	+	+	+	+	+	+	3	D86967
0213[g]	4,990	1,491	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6	D86968
0214[e,f,g]	4,550	757	+	+	+++	+	+	+	+	+++	+	+	+	+	+	+	+	+	+	+	1	D86987
0215[f]	4,935	823	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3,X	D86969
0216[f,g]	6,479	1,581	+	+	+	+	+	+	+	+++	+	+	+	+	+	+	+	+	+	+	17	D86970
0217	5,404	673	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	10	D86971
0218[f,g]	4,689	761	+	+	+	+	+	++	+	+	+	+	+	++	+	+	++	+	+	++	3	D86972
0219[e,f]	7,819	2,412	+	−	+	+/−	+	+	+	++	+	+	+	+	+	+	+	+	+	+	6,12	D86973
0220	5,471	553	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	14,16	D86974
0221[f,g]	5,311	1,129	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19	D86988
0222[f,g]	6,033	1,163	+	−	+	+	+	+	+	+	+	+	+	+	+	++	+	+	−	+	18	D86975
0223[f,g]	4,121	1,165	++	−	++	+	+	+	+	+	+	+	++	++	+	+	+	+	+	++	19	D86976
0224[f,g]	4,226	1,227	+	−	+	+	+	+	+	+	+	−	+	+	+	++	+	+	+	+	16	D86977
0225[e,f]	6,237	2,013	+	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	7	D86978
0226[e]	5,891	751	+	+	+	+	+	+	+/−	+	+	+	+	+	+	+	+	+	+	+	3	D86979
0227	5,217	336	++	++	++	+	+	+	+	++	+	++	+	+	+	+	+	+	+	+	14	D86980
0228[e]	6,465	681	+	+	+	+	+	+	n.d.	+	+	+	+	+	+	+	+	+	+	+	17	D86981
0229[f]	6,335	1,180	+++	+++	+++	+	+	+	+	+++	+	+++	+	+	+	+	+	+	+	+	6	D86982
0230[e,f]	5,510	1,496	+	+	++	−	++	++	+	+	+	+	+	+	+	+	++	+	+	−	2	D86983
0231[f]	6,248	476	+	+	+/−	+	+/−	+/−	+/−	+/−	+/−	+/−	+	+	+	+	+	+	+	+	1	D86984
0232	6,025	1,008	+	+	++	+	+	−	+	++	+	+	+	+	+	+	+	+	+	+	4	D86985
0233[e,f,g]	6,368	2,035	+	+	+	+/−	+	+	+	+	+	+	+	+	+	+	+	+	+	++	16	D87071
0234[f]	5,134	1,482	+	+	+	+	+	+	+	+	−	+	+	++	+	+	+	+	+	+	Y	D87072
0235[f]	5,399	850	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2	D87078
0236[f,g]	5,878	1,687	+	+	+	+	+	+	+	++	+	+	+	+	+	++	+	+	+	+	2*	D87073
0237[f,g]	7,239	308	+	−	+	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1*	D87074
0238[e,f]	5,608	330	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20*	D87075
0239[f]	5,630	571	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	5	D87076
0240	6,060	983	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	6*	D87077
0241[f]	6,371	522	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	7*	D87682
0242[e,f]	3,760	529	+	+	+	+	+	+	++	++	+	+	+	+	+	+	+	+	+	+	2*	D87684
0243	6,984	699	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+/−	+	9*	D87683
0244[f]	5,975	1,723	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6*	D87685
0245[e,f]	6,296	515	+	+	+	+	+	+	−	+	+	+/−	+	++	+	+	+	+	+	+	16*	D87432
0246[e,f,g]	6,777	2,212	+	+	−	−	+	++	+	+	+	+/−	++	+/−	+/−	+/−	+	+	−	++	3*	D87433
0247[e]	5,338	303	+	+	+	+	+	+	+	+	+	+/−	+	+	+	+	+	+	+/−	+	14*	D87434
0248[e,f,g]	5,634	1,691	+	+	+	+	+	+	+	++	+	+	+	+	+	+	+	+	+	+	10*	D87435
0249[f]	6,219	896	+	+	+	+	+	+	++	+/−	++	+	+	+	+	+	+	+	+/−	+	18*	D87436
0250[e,g]	5,082	802	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1*	D87437
0251[f]	3,875	820	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16*	D87438
0252[f]	4,288	664	+	+	+	+	+	+	+	++	+	+	+	+	+	+	+	+	+	+	15*	D87440
0253[e]	2,805	708	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	1*	D87442
0254[e]	6,049	992	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	11*	D87443
0255[e,f]	4,028	625	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20	D87444
0256[g]	6,935	635	+	+/−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+/−	+/−	15*	D87445
0257[e,f,g]	6,178	1,805	+	+	+	+	+	+	+	++	+	+	+	+	+	+	+	+	+	+	2*	D87446
0258	6,313	391	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	9*	D87447
0259[f]	5,298	1,550	+	+/−	+	+	+	+	+	+	+	+	+	+	+	++	+	+	+	+	3*	D87448
0260[e,f]	5,918	383	+	+	+	+/−	+	+	++	+	+	+	+	+	+	+	+	+	+	+	1*	D87449
0261[f]	6,155	1,287	+	+	+/−	+/−	+	+	+	+	+	+	+	+	+	+	+	+	+/−	+	10*	D87450
0262[g]	3,205	761	++	++	+++	+	+	+	+	+++	+	++	+	+	+	++	+	+	+	+	12*	D87451
0263[f]	4,461	441	+	+	+	+	+	+	+	+	+	+	+	+	+	++	+	+	+	+	3*	D87452
0264	2,635	415	++	++	+++	+	+	+	+	+++	+	+	+	+	+	+	+	+	+	+	5*	D87453
0265	5,551	401	+	+	+	+	+	+	n.d.	++	+	+	+	+	+	+	+	+	+	+	7*	D87454
0266[f]	5,585	766	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13*	D87455
0267[e,f]	4,408	666	+	+	+	++	+	+	+	++	+	+	+	+	+	+	+	+	+	+	X*	D87743
0268[e,f]	5,976	1,193	+	+	+	+	+	+	+	+	+	+	+	+	+	++	+	+	+	+	1*	D87742
0269[f]	2,625	559	−	−	−	+++	−	−	−	−	+/−	+/−	−	+/−	−	++	+	+/−	+	+/−	6*	D87459
0270[g]	2,552	345	+	+	+	++	+	+	+	+	+	+	+	+	+	+	++	+	+	−	19*	D87460
0271[e,f,g]	3,542	193	+	+	+++	+++	+	+	+	+	+	+++	+	+	++	++	+	+	++	+	14*	D87461
0272[f]	3,474	726	+	+	++	++	+	+	+	+++	+	+	+	+	+	+++	+	++	++	+	3*	D87462
0273	3,040	330	−	−	−	+++	−	−	−	−	−	−	−	−	+/−	+	+/−	+/−	+/−	−	8*	D87463
0274[e,f]	3,010	907	+	+	+	+	+	+	+	+	+	+	+	+	+	++	+	+	+	+	6*	D87464
0275[e,f,g]	5,316	424	+	+	+	++	+/−	+	−	+	+	−	+	++	+/−	+	+	+	−	++	10*	D87465
0276[f]	4,185	309	n.d.	n.d.	n.d.	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4*	D87466

Table 3. Continued.

Gene number (KIAA)	Total length of cDNA (bp)[a]	Amino acid residues	Expression[b] KG-1	HeLa	He	Br	Pl	Lu	Li	Sk.m	Ki	Pa	Sp	Th	Pr	Te	Ov	Sm.i	Co	Pe.b	Chromosomal[c] location	Accession[d] number
0277[f]	5,900	580	−	−	+/−	+	+/−	+/−	−	−	−	+/−	+	−	−	+	−	+/−	−	−	7*	D87467
0278[f]	2,935	460	−.	−	+	+	−	+	−	+	−	+	−	−	+	+	+/−	+/−	+/−	+/−	8*	D87468
0279[e,f,g]	8,924	2,408	−	−	+/−	++	−	−	−	+	+	+/−	−	−	+	++	−	−	+/−	+/−	1*	D87469
0280	6,837	291	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	11*	D87470

n.d., not determined; He, heart; Br, brain; Pl, placenta; Lu, lung; Li, liver; Sk.m., skeletal muscle; Ki, kidney; Pa, pancreas; Sp, spleen; Th, thymus; Pr, prostate; Te, testis; Ov, ovary; Sm.i, small intestine; Co, colon; Pe.b, peripheral blood leukocytes.

a) Values excluding poly(A) sequences.

b) Expression of mRNA in indicated cells and human tissues (Clontech, USA) was examined by northern hybridization, and the strength of the positive signals are indicated (+/−, +, ++, +++).

c) Asterisks indicate that choromosome localization has been determined only by radiation hybrid mapping. In the others, the panels of both radiation hybrid and human-rodent hybrid were used.

d) Accession number of GSDB, DDBJ, EMBL and NCBI nucleotide sequence databases.

e) Putative transmembrane domains were contained (see Supplemental pages).

f) Similarities to known genes were identified (see **Table 1** and Supplemental pages).

g) Protein motifs were recognized (see **Table 2** and Supplemental pages).

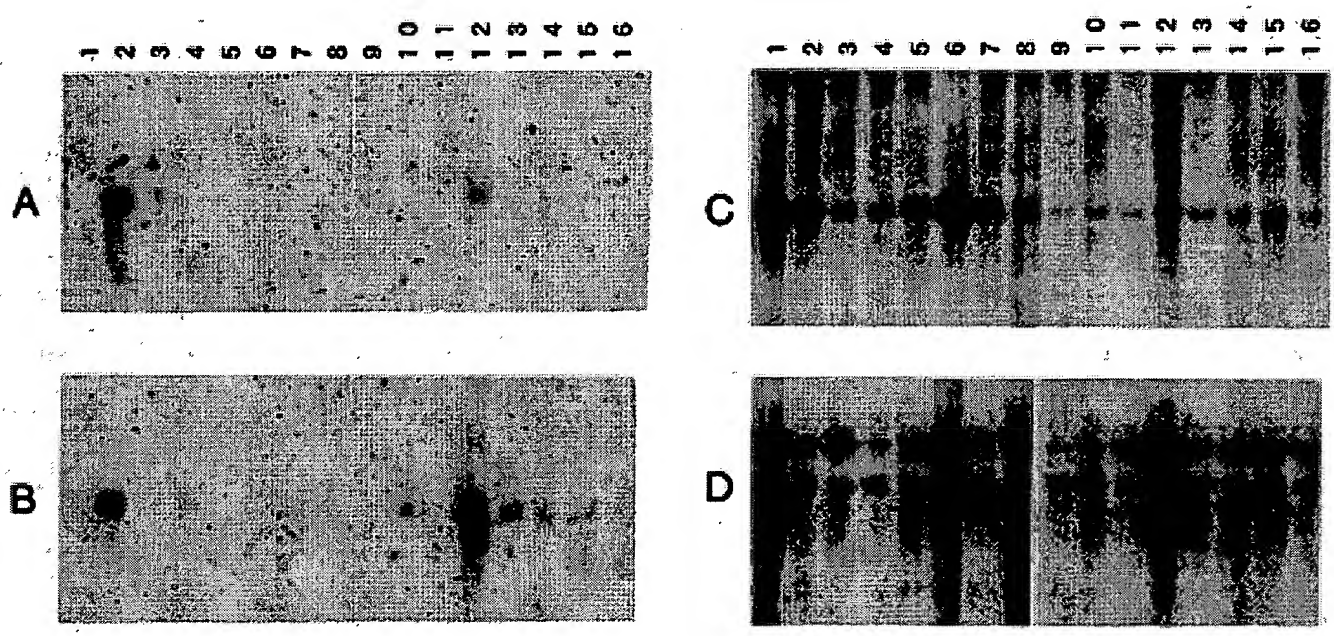


Fig. 5. The typical expression patterns of representative genes. cDNA fragments were randomly labeled and hybridization was carried out as described previously. Human MTN blots were purchased from CLONTECH Laboratories, Inc.. **A**, KIAA0273; **B**, KIAA0269; **C**, KIAA0264; **D**, KIAA0262. Lane 1, heart; 2, brain; 3, placenta; 4, lung; 5, liver; 6, skeletal muscle; 7, kidney; 8, pancreas; 9, spleen; 10, thymus; 11, prostate; 12, testis; 13, ovary; 14, small intestine; 15, colon; 16, peripheral blood leukocyte.

clones yielded relatively strong signals in both heart and skeletal muscle (as shown in Figs. 5C and D, lanes 1 and 6).

The chromosomal location of these genes has been determined by the panels of radiation hybrid[6] and/or human-rodent hybrid cell lines (see Table3).[1]

Acknowledgments: This project was supported by grants from the Kazusa DNA Research Institute Foundation.

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Second Edition

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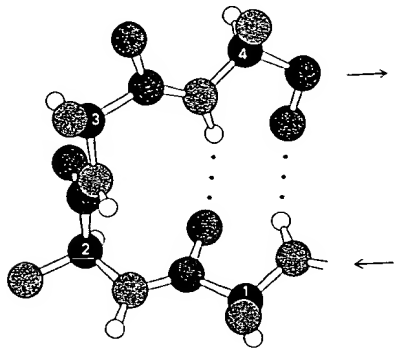


Figure 2-42
Structure of a β-turn. The CO group of residue 1 of the tetrapeptide shown here is hydrogen bonded to the NH group of residue 4, which results in a hairpin turn.

POLYPEPTIDE CHAINS CAN REVERSE DIRECTION BY MAKING β-TURNS

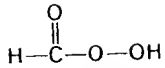
Most proteins have compact, globular shapes due to frequent reversals of the direction of their polypeptide chains. Analyses of the three-dimensional structures of numerous proteins have revealed that many of these chain reversals are accomplished by a common structural element called the *β-turn*. The essence of this hairpin turn is that the CO group of residue n of a polypeptide is hydrogen bonded to the NH group of residue $(n + 3)$ (Figure 2-42). Thus, a polypeptide chain can abruptly reverse its direction.

LEVELS OF STRUCTURE IN PROTEIN ARCHITECTURE

In discussing the architecture of proteins, it is convenient to refer to four levels of structure. *Primary structure* is simply the sequence of amino acids and location of disulfide bridges, if there are any. The primary structure is thus a complete description of the covalent connections of a protein. *Secondary structure* refers to the steric relationship of amino acid residues that are close to one another in the linear sequence. Some of these steric relationships are of a regular kind, giving rise to a periodic structure. The α helix, the β pleated sheet, and the collagen helix are examples of secondary structure. *Tertiary structure* refers to the steric relationship of amino acid residues that are far apart in the linear sequence. It should be noted that the dividing line between secondary and tertiary structure is arbitrary. Proteins that contain more than one polypeptide chain display an additional level of structural organization, namely *quaternary structure,* which refers to the way in which the chains are packed together. Each polypeptide chain in such a protein is called a *subunit*. Another useful term is *domain,* which refers to a compact, globular unit of protein structure. Many proteins fold into domains having masses that range from 10 to 20 kdal. The domains of large proteins are usually connected by relatively flexible regions of polypeptide chain.

AMINO ACID SEQUENCE SPECIFIES THREE-DIMENSIONAL STRUCTURE

Insight into the relation between the amino acid sequence of a protein and its conformation came from the work of Christian Anfinsen on ribonuclease, an enzyme that hydrolyzes RNA. Ribonuclease is a single polypeptide chain consisting of 124 amino acid residues (Figure 2-43). It contains four disulfide bonds, which can be irreversibly oxidized by *performic acid* to give cysteic acid residues



Performic acid

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/425,501	10/22/1999	ROBERT MARK	GNN-005	9642

AM1600 12

25291 7590 02/05/2003

WYETH
PATENT LAW GROUP
FIVE GIRALDA FARMS
MADISON, NJ 07940

EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	24

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Due 5/5/03

Office Action Summary	Application No.	Applicant(s)	
	09/425,501	MARK ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- *The MAILING DATE of this communication appears on the cover she t with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-13,16-21,43,44 and 49-65* is/are pending in the application.

4a) Of the above claim(s) *5-13 and 16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-44, 49-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachm nt(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 23.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' response to the office action (Paper No. 22) filed on November 4, 2002 has been entered and considered.

2. The IDS (Paper No. 23) filed on November 4, 2002 has been entered and considered.

Response to arguments

3. Applicants' response to the office action (Paper No. 22) is fully considered and found persuasive in part.

4. The Declaration submitted under 37 C.F.R. 1.132 has been considered and found not persuasive. The Declaration shows citations of NCBI Blast search for an isolated nucleic acid and amino acid sequence homology (99-100%) obtained from a mouse clone. The NCBI blast search exhibits are fully considered. As per the "85% language", the declaration is found persuasive, however the showings do not commensurate with the newly amended claims drawn to human isolated nucleic acid and corresponding amino acid sequence, the disclosure of Nagase et al. is from a human clone and hence the disclosure of Nagase et al. is operable in the instant context. MPEP 2121.02 notes "One of ordinary skill in the art must be able to make or synthesize" regarding operativeness of products. Here, Nagase et al. in fact synthesizes the nucleic acid, and an ordinary practitioner in molecular biology could synthesize any known sequence using a selection from any of a garden variety of extremely well known methods ranging from simple chemical synthesis to ligation to PCR amplification with 100% expectation of success.

5. With respect to the rejection made in the previous office action under 35 USC 102(b), Applicants' amendment and arguments have been fully considered and found not persuasive.

Applicants argue that the prior art of the record (Nagase et al.) does not provide any enablement for the isolated nucleic acid, which has 100% homology with the instant SEQ ID Nos. 1, and 2. This argument is fully considered and found not persuasive because enablement issue is not relevant in the present context. It is concerned with whether the reference is operable or not. The prior art teaches the nucleotide sequence which is within the public domain. As stated in MPEP 2121.02, "ONE OF ORDINARY SKILL IN THE ART MUST BE ABLE TO MAKE OR SYNTHESIZE", one could able to chemically synthesize the sequence, ligate and amplify the product based on the prior art information and is can make the compound operable. MPEP 2121.02 further states "a reference is presumed operable until applicant provides facts rebutting the presumption of operatibility. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Therefore, applicant must provide evidence showing that a process for making was not known at the time of the invention. The citations to the utility guidelines is irrelevant because the prior art is not required to be useful to anticipate. The chemical sequence is known in the art as disclosed by Nagase et al. Thus the reference is operable under ordinary circumstances. Therefore, the rejection is maintained herein. New claims 62-65 are also rejected herein under 35 USC102(b) as anticipated by Nagase et al. because the said isolated nucleic acid of Nagase et al. meets the limitations regarding Bcl-xL binding properties as discussed above and homology greater than 91% to the said nucleic acid (see sequence alignment provided in the previous office action).

6. With respect to the rejection made in the previous office action under 35 USC 112 first paragraph, Applicants' arguments (Paper No. 22) are considered, but found persuasive in part. Applicants' arguments and amendment of the instant claim 49, with regards to homology is fully considered and found persuasive. The objection to the "85% language" is withdrawn herein to

the instant claim 49, however for hybridizable fragments and position of binding activity of said isolated nucleic acid under hybridizable conditions, the argument is not convincing. By permutation and combination, there would be over several thousand possible fragments, if not millions as discussed in the earlier office action. With regards to the arguments to the identity of biological function in the said nucleotide or peptide of SEQ ID Nos. 1 and 2, it is not sufficient enough to identify where in the sequence the biological function resides or position of amino acids responsible for the biological activity. Applicants' suggestion to note the specification for the teaching of structure / function relationship is fully considered, but the limitation is not found in the claims. Specification cannot be read into the claims. Therefore, the rejection is maintained herein. New claims 62-65 are also rejected herein under 35 USC 112, first paragraph, since the new claims 62-65 are dependent on the independent claim 52, which was rejected in the previous office action and the rejection is maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
January 31, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER

ostitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	09/425,501
Filing Date	October 22, 1999
First Named Inventor	Mark, R.T.
Group Art Unit	1637
Examiner Name	Suryaprabha Chunduru
Attorney Docket Number	AM100012OX1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	U.S. Patent Document Number (If known)	U.S. Patent Document Kind Code (If Known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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Examiner Initials*	Cite No.	Foreign Patent Document Office	Foreign Patent Document Number	Foreign Patent Document Kind Code (If Known)	Name of Patentee or Applicant of Cited document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
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OTHER PRIOR ART — NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
SRC	1.	BENACHENHOU, N. et al., "Characterization and expression analyses of the mouse Wiskott-Aldrich syndrome protein (WASP) family membe Wave1/Scar," Gene (2002), 131-140, 290, Elsevier Science B.V.	☐
SRC	2.	BLAST search (www.ncbi.nlm.nih.gov/blast/Blast.cgi) for nucleotide sequence	☐
SRC	3.	BLAST search (www.ncbi.nlm.nih.gov/blast/Blast.cgi) for protein sequence	☐

Examiner Signature	Suryaprabha Chunduru	Date Considered	1/30/03

CC: PRINCETON / BTB AM 100012

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/425,501	10/22/1999	ROBERT MARK	GNN-005	9642

25291 7590 05/07/2002

WYETH
FIVE GIRALDA FARMS
MADISON, NJ 07940

EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	

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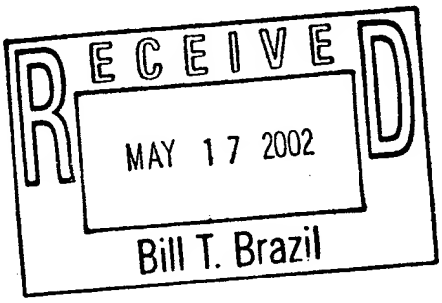

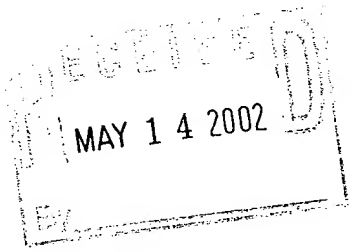

DOCKETED 8-7-02
DUE DATE
BY: 5/15/02

PTO-90C (Rev. 07-01)

Notice of References Cited	Application/Control No. 09/425,501	Applicant(s)/Patent Under Reexamination MARK ET AL.	
	Examiner Suryaprabha Chunduru	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

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	L	US-			
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Nagase T et al. Prediction of the coding sequences of unidentified human genes. VI. The coding sequences of 80 new genes deduced by anlysis of cDNA clones from cell line KG-1 and brain. DNA Res., vol. 3: 321-329, 1996.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Offic Action Summary	Application No.	Applicant(s)	
	09/425,501	MARK ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-13,16-21,43,44 and 49-61* is/are pending in the application.

4a) Of the above claim(s) *5-13 and 16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,44 and 49-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgement is made for the request to establish continued prosecution application (CPA) (Paper NO. 20) filed on March 12, 2002. The request for CPA is accepted and is established with the status of the application as follows:

a. the filling date of this CPA is established as 10/22/1999;

b. Claims 42-43 are pending. Claims 22-42 and 45-48 are canceled. New claims 49-61 are added.

2. Applicants' response to the earlier office action (Paper No. 18) filed on March 12, 2002 has been entered.

Response to Arguments

3. Applicant's response to the office action (Paper No.12) is fully considered and found persuasive in part.

4. The Declaration submitted under 37 C.F.R. 1.132 has been considered and found not persuasive. The Declaration argues that the Nagase et al reference is not enabled to use the nucleic acid sequence disclosed. However, with regard to the operativeness of the reference, the issue is not whether the reference enables use of the product, but rather whether the reference enables synthesis of the product. As MPEP 2121.02 notes "One of ordinary skill in the art must be able to make or synthesize" regarding operativeness of products. Here, Nagase et al. in fact synthesizes the nucleic acid, and an ordinary practitioner in molecular biology could synthesize any known sequence using a selection from any of a garden variety of extremely well known methods ranging from simple chemical synthesis to ligation to PCR amplification with 100% expectation of success.

5. With respect to the rejection made in the previous office action under 35 U.S.C. 102(b), Applicant's arguments with respect to claims 43-44 have been considered but are found not persuasive because (i) the declaration is not persuasive with regards to the instant claims as noted above (ii) Applicants argument that the disclosure of Nagase et al. did not enable to make and use of the sequence is not persuasive since As stated in MPEP 2121.02, "ONE OF ORDINARY SKILL IN THE ART MUST BE ABLE TO MAKE OR SYNTHESIZE", one could able to chemically synthesize the sequence, ligate and amplify the product based on the prior art information and is can make the compound operable. MPEP 2121.02 further states "a reference is presumed operable until applicant provides facts rebutting the presumption of operatibility. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Therefore, applicant must provide evidence showing that a process for making was not known at the time of the invention.

Further, the sequence disclosed by Nagase et al. is from human brain cells. Thus, the (100%) homology shown in the earlier office action is with instant SEQ ID NO.1, but not with corn species as stated by the applicants in response to the office action.

The citations to the utility guidelines is irrelevant because the prior art is not required to be useful to anticipate. Thus the rejection is maintained herein.

New issues

5. Claims 43-44 and new claims 49-61 are pending and are considered for examination in this office action.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-53 and 57-59 are rejected under 35U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claim 49 is drawn to a genus (fragments) of Bcl-xL nucleic acid comprising a nucleic acid encoding 85% amino acid homology to SEQ ID NO: 2, claim 50 drawn to a binding domain which hybridizes to a complement of a nucleotide sequence SEQ ID NO.1 and a nucleic acid encoding Bcl-xL binding protein as shown in SEQ ID NO.1. This large genus is represented in the specification by the named SEQ ID Nos. 1 and 2. Thus, applicant has expressed possession of only one species in a genus, which comprises hundreds of millions of different possibilities. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the sequences are disclosed in the sequences with 85% homology. With regard to the sequences, which have 85% homology, this is insufficient to demonstrate identity of Bcl-xL binding and function where no structural information regarding where in the protein the binding and function resides. The recitation of amino acids 419-559 or 429-559 in Bcl-xL binding domain in claim 53 do not specify the exact site for binding and the activity of the protein. Further no information is given regarding a methodology to determine such common elements or attributes. Further, for hybridization purposes, even a fragment of any length which comprises partial sequence of SEQ ID NO.1 hybridizes with the SEQ ID NO. 1. It is not necessary to have a full length sequence of

the said SEQ ID NO. 1 for hybridization. Thus, there is no description of fragments or complementary nucleic acid sequence that hybridize to SEQ ID NO. 1.

With regard to the written description, all of these claims encompass nucleic acid sequences different from those disclosed in the specific SEQ ID Nos: 1 and 2 which include modifications by permitted by the 85% language for which no written description is provided in the specification.

> It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the amino acid sequence of the disclosed SEQ ID Nos are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any amino acids modified by addition, insertion, deletion, substitution or inversion with the disclosed SEQ ID Nos but retaining correlative function in the claimed product.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 49-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase et al. (DNA Res., 3: 321-329, 1996).

Nagase et al. teaches the coding sequence of cDNA clone from human myeloid cell line KG-1 and brain wherein Nagase et al. disclose a cDNA clone which is identical or absolute homology (100%) to the claimed sequences in SEQ ID Nos. 1 and 2 of the instant invention (see sequence alignment from GenEmbl. and Swissprot_39 databases). Nagase et al. also disclose that the cDNA clones showed homology to the genes that play key roles in regulation of developmental stages, apoptosis and cell-to-cell interaction (see page 321, abstract). Thus the disclosure of Nagase et al. meets the limitations in the instant claims.

No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 703-308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
April 30, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER

BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Gavin Bogle is hereby given limited recognition under 37 CFR §10.9(b) as an employee of Wyeth, to prepare and prosecute patent applications wherein the assignee of record of the entire interest is Wyeth (formerly American Home Products Corporation), Wyeth-Ayerst Laboratories, Wyeth-Ayerst International, Inc., Wyeth-Ayerst Research, or Genetics Institute. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Gavin Bogle ceases to lawfully reside in the United States, (ii) Gavin Bogle's employment with Wyeth ceases or is terminated, or (iii) Gavin Bogle ceases to remain or reside in the United States on an H-1B visa.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: July 9, 2004

Harry I. Moatz
Director of Enrollment and Discipline